Speaking from the Heart: Systemic Copper Signaling

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Copper is a ubiquitously essential nutrient for cells. In this issue of *Cell Metabolism*, Kim et al. (2010) demonstrate that tissue copper status can be communicated across organ systems. In a mouse model for cardiac copper deficiency, a serum-carried signal mobilized liver and intestinal copper by inducing ATP7A, a copper-exporting ATPase.

Copper is an essential nutritional trace element that is widely employed as a cofactor for enzymes acting in oxygen chemistry and electron transfer. Although less abundant in cells than other essential metals such as iron and zinc, copper is broadly used in reactions that span the functions of respiration, antioxidant defense, pigment and connective tissue formation, neurotransmitter synthesis, and iron oxidation. In mammals, the manifestations of copper deficiency are numerous and range from neurological and hematological disorders to connective tissue deficits (Madsen and Gitlin, 2007; Tao and Gitlin, 2003). Given the biological importance of copper, intense research has focused on the molecular pathways for copper metabolism. This has identified cell-surface and intracellular copper transporters, as well as soluble copper chaperones that ferry the metal to key destinations in the cell (Barry et al., 2010; Kaplan and Lutsenko, 2009; Robinson and Winge, 2010). A great deal, therefore, is known about copper homeostasis at the single-cell level. Yet in multicellular species, control of copper metabolism must extend beyond the cell and cross multiple organ systems.

In mammals, the bulk of dietary copper absorbed by the intestine rapidly enters the liver, where the metal is then eliminated through the bile. Only a fraction of dietary copper enters the circulation for distribution to peripheral organs (Madsen and Gitlin, 2007; Tao and Gitlin, 2003). Except in extreme cases of genetic disorders of copper transport (e.g., Wilson's and Menkes diseases, described below), copper homeostasis operates to near perfection. Irrespective of large fluctuations in dietary copper, the metal is adequately delivered to peripheral organs and properly eliminated to prevent toxicity from copper overload (Kaplan and Lutsenko, 2009; Madsen and Gitlin, 2007; Tao and Gitlin, 2003). Such elegant homeostasis of the metal is sure to involve cross-organ communication, but to date direct evidence for systemic copper signaling has been lacking.

Work in this issue (Kim et al., 2010) now provides evidence for a systemic signaling mechanism to control copper metabolism. This somewhat serendipitous finding originated in the study of a mouse model for cardiac copper deficiency. The $Ctr1^{hrt/hrt}$ mouse specifically lacks, in cardiac tissue, the Ctr1 high-affinity copper transporter. This mouse with low cardiac copper presented with the anticipated severe dilated cardiomyopathy. However, as a surprising outcome, the mice also exhibited a striking decline in liver levels of copper and a concomitant rise in serum copper. Evidently, the animals responded to cardiac copper deficiency by elevating circulatory copper at the expense of liver copper stores (Figure 1).

Studies of the underlying mechanism pointed to changes in expression of the Cu efflux pump, ATP7A. In the gastrointestinal tract, this copper-transporting ATPase normally functions to transfer copper across the basolateral membrane of intestinal epithelial cells, thus ensuring the delivery of dietary copper into the portal circulation. Adult liver does not normally express ATP7A to any significant degree but instead expresses the homologous ATP7B Cu transporter that facilitates copper export into the bile (Barry et al., 2010; Kaplan and Lutsenko, 2009; Madsen and Gitlin, 2007; Tao and Gitlin, 2003). Fine-tuned expression of ATP7A and ATP7B is essential for copper homeostasis. Inherited mutations in ATP7A lead to a fatal disorder of copper deficiency (Menkes disease), and ATP7B mutations cause a familial copper overload syndrome of the liver (Wilson's disease) (Barry et al., 2010; Kaplan and Lutsenko, 2009; Madsen and Gitlin, 2007; Tao and Gitlin, 2003). Although the ATP7A gene appears silent in normal liver, the $Ctr1^{hrt/hrt}$ mouse in the present study by Kim et al. exhibited a striking increase in expression of liver ATP7A, and the transporter was also induced in the intestine (Kim et al., 2010). Evidently, copper deficiency in the heart signaled an adaptive stress response to mobilize copper from the liver and intestine via the action of ATP7A. Prior to this study, liver was not known as a storage organ for copper, only as a vehicle for eliminating copper through the bile. The induction of liver ATP7A with cardiac copper deficiency unveiled a new pool of liver copper that is capable of being mobilized. Even more striking was the evidence that such activation of liver ATP7A involved a certain soluble serum factor. Indeed, serum from the $Ctr1^{hrt/hrt}$ mouse was seen to induce ATP7A expression in cells in culture (Kim et al., 2010).

A previous precedent for systemic metal signaling is the iron-responsive peptide hormone hepcidin. Iron overload, inflammatory conditions, and the unfolded protein response all signal the liver to produce and release hepcidin into circulation. Serum hepcidin then targets intestinal and macrophage cells, where it acts to block iron release from the iron export protein ferroportin (De Domenico and Kaplan, 2009; Ganz, 2008). Based on the current report by Kim et al. (2010), we now know that cross-organ communication of metal status is not unique to iron.

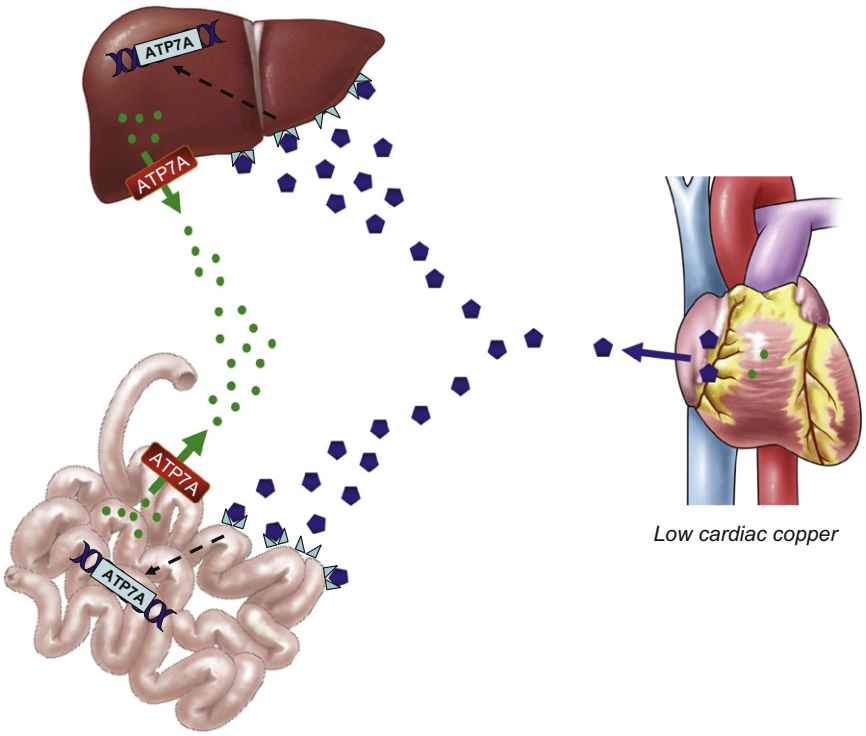

Figure 1. Systemic Signaling of Cardiac Copper Status
In *Ctr1*$^{hrt/hrt}$ mice, cardiac copper deficiency signals a stress response to mobilize copper stores from the intestine and liver. A response factor (blue pentagons) is proposed to be released from the heart into circulation where it can target receptors (light blue) on the liver and intestine. Activation of these receptors signals the induction of the ATP7A gene (dotted arrow) encoding the Cu-transporting ATPase (orange box) that acts to export tissue copper (green dots) into circulation. Artwork assistance is by Kate Mahan.

Tissue copper status can likewise be sensed and signaled to organs at a distance via a specific serum-response factor.

The findings by Kim et al. (2010) will undoubtedly foster new directions for studies of copper metabolism. For example, what is the signaling molecule? Perhaps this represents a new peptide hormone that targets a liver- and intestinal-specific receptor for controlling ATP7A expression (Figure 1). And is this signal specific for cardiac copper deficiency? The heart has a particularly high demand for copper through mitochondrial respiration, but the same can be said for neurological and muscle tissue. It is conceivable that deficits in copper from a variety of organs will elicit an "SOS" response to mobilize copper stores. Additionally worth pursuing is the newly revealed storage pool of copper in the liver. In what form is the copper stored? Is it sequestered in secretory vesicles or bound to proteins such as metallothionein? Lastly, now that systemic signals are evident for both copper and iron, will the same hold true for other inorganic nutrients such as zinc and manganese? The potential toxicity of these essential heavy metals would seem to justify a cross-organ signaling system of control. Future studies are likely to reveal a host of serum-response factors that serve to communicate tissue metal status and facilitate proper adaptive responses.

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